DEVELOPMENT OF A LARGE-SCALE COMPUTER HEART MODEL FOR SUPPORTING CLINICAL STUDIES OF ARRHYTHMIAS

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***Abstract*- Although a large number of studies on cardiac electrical properties have been conducted, it remains difficult to integrate all fragmented data into one unified framework. As an approach to this, we developed a large-scale (6 x 10^6 elements) three-dimensional simulator of cardiac electrical activity based on human ventricular geometry and experimentally derived ionic channel models. This simulator has the advantages over previous simulators in that ventricular fibrillation can be induced with clinical programmed extrastimulation, fibrillation can be induced more easily by extrastimulation at right ventricular outflow tract as in clinical situation, and it is possible to examine the contribution of early afterdepolarization to arrhythmogenecity in patients with e.g., long QT syndrome. These advantages indicate that our simulator is useful in supporting a wide range of clinical studies of arrhythmias.**

Keywords*- Fatal arrhythmia, Computer simulation, Ionic channel model

I. INTRODUCTION

Various types of arrhythmias occur as a result of abnormalities in cardiac electrical properties. These properties include those at different scale levels, from gene, ionic channels, and myocardial cells, up to the level of the heart as an organ. All of these are likely to contribute to the genesis of arrhythmias. To combat fatal arrhythmias, a large number of studies on cardiac electrical properties and activities have been conducted. Despite such plentiful information, it is not possible to reconstruct the electrical activity of a heart as a whole, or to predict the occurrence of clinical arrhythmias. This inability has resulted in drugs paradoxically aggravating the occurrence of fatal antiarrhythmias when they are designed to provide benefit from the viewpoint of ionic channels and cells. In addition, there are no means to identify the patients at high risk of fatal arrhythmias. It remains difficult to integrate the elementary data into ine single framework to avoid such problems.

Accordingly, we made use of the so-called number crunching ability of computer to integrate data obtained at various scale levels. We developed a large-scale three-dimensional simulator of cardiac electrical activity based on human ventricular geometry and ionic channel models, derived from experimental data. We tested the clinical utility of this simulator by examining the relationship between the site of extrasystoles and the arrhythmogenecity of ventricular fibrillation.

II. METHODOLOGY

A. Simulator

We developed a simulator, comprising 5.64 million units [1, 2], each of which behaves according to the ionic channel model (see below). Each unit corresponds to the cube 0.258 mm in either direction. These units are arranged in a three-dimensional space (300 x 300 x 300) according to human ventricular geometry. For normal hearts we assumed that electrical properties of all units are the same (homogenous) and isotropic.

B. Ionic channel model

We used the model developed by Luo and Rudy [3] to express the behavior of each unit. The model consists of the differential equations between 8 state variables. It incorporates major ionic currents such as I_{Na}, I_{Ca}, I_{Kr}, I_{Ks}, and I_{K1}. The model is known to reproduce a physiological action potential duration, voltage, and form.

C. Computation

We used a supercomputer (SX-4/16, 8 of 16 CPU allocated, NEC, Tokyo, Japan) for the simulation. We accelerated the performance of the simulator by various means [2], such as, vectorization, parallel processing, piecewise linear interpolation of nonlinear functions, and linearization of the three-dimensional array. A Combination of these acceleration techniques shortened the calculation time by a factor of ~3000. It was ~9000 times as fast as a Pentium III 500 MHz personal computer. The performance

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of the supercomputer was almost maximized judging from the vectorization ratio of 99.6%, and the mean vector length of 255.9 for 256-length vector.

D. Examination of the relationship between the site of extrasystoles and the arrhythmogenecity of ventricular fibrillation

It is known that electrical properties are inhomogeneous within the ventricle. Although clinical as well as experimental findings have revealed that exceedingly large inhomegeneity contributes to the arrhythmogenecity of ventricular fibrillation, it is unknown if the geometry of the media (i.e., myocardial wall) per se affects the arrhythmogenecity. To explore this, we imposed programmed extrastimulation from the pacing site of both the ventricular apex and right ventricular outflow tract and compared the arrhythmogenecity. With extrastimulation up to 3 premature contractions, we tried all possible stimulation patterns, as performed in the clinical induction of tachyarrhythmias. In an attempt to determine the mechanisms involved, we repeated a similar programmed extrastimulation in a more simple form of medium. We examined a cube, a rectangular form with sides of two different lengths and one with sides of three different lengths.

III. Results

Fig. 1 illustrates the activation pattern of ventricles after the induction of ventricular fibrillation with programmed extrastimulation; in a similar way we examined the inducibility of ventricular fibrillation in clinical settings. Although apical extrastimulation induced fibrillation with only limited stimulation patterns (left panel), extrastimulation from the ventricular outflow tract induced spiral waves more easily. These spiral waves are repeatedly fragmented into multiple waves and sustained (right panel).

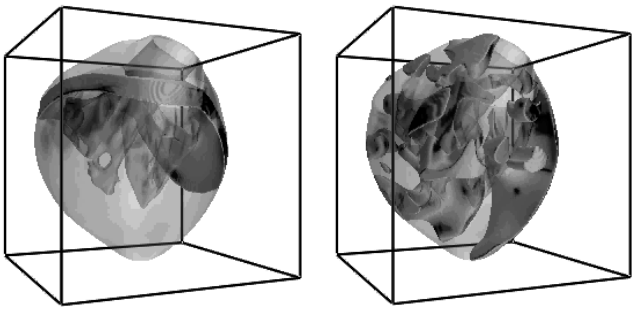

Fig. 1. Activation patterns of ventricles after induction of ventricular fibrillation with programmed extrastimulation from apex (left), and from right ventricular outflow tract (right).

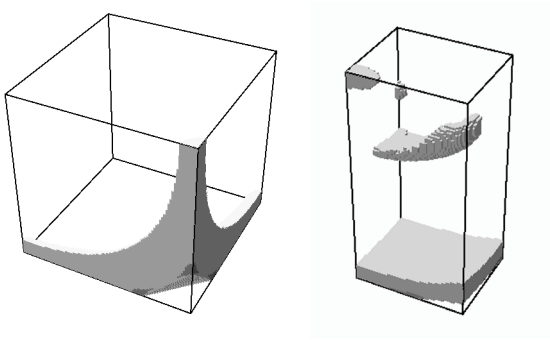

Fig. 2. Activation patterns of media after induction of fibrillation with programmed extrastimulation. Both cube (left) and rectangular form with sides of three different lengths (right) are examined.

Similar examination in more simple form of media revealed that spiral waves were not induced in cubes, but in rectangular form with sides of three different lengths (Fig. 2).

IV. Discussion

We have shown in the present study that fibrillation inducibility is not uniform between different sites for imposing extrastimulation. This result can only be obtained with a simulator with ventricular geometry. Examination in more simple form of medium indicated that the existence of a multiplicity of medium length is important in fibrillation inducibility, though fibrillation persisted only in more complex geometry as in that of actual ventricles.

Our simulator has several characteristics; it is a large-scale, three-dimensional, ionic channel-based simulator that takes ventricular geometry into consideration. Because our simulator has all these characteristics mentioned, unlike other simulators, there are advantages for its use in clinical studies besides the fact that a large-scale, three-dimensional simulator is necessary to maintain the number of spiral waves evident in typical ventricular fibrillation.

The use of the realistic ventricular geometry of the human heart made it possible to induce ventricular fibrillation with programmed extrastimulation (PES) from a single pacing site as is used clinically. This is in contrast with inducing fibrillation with cross-filed stimulation in simulation in medium of a more simple geometry. This study indicates that fibrillation can be induced in a near normal heart without excessive inhomogeneity; this is also reported clinically as a limitation of PES.

Due to the complex ventricular geometry, the inducibility of fibrillation was quite different between PES from different pacing sites, as shown in the Results. Clinical induction of fibrillation from the right ventricular outflow tract is considered less specific.

These advantages indicate that our simulator is useful in supporting a wide range of clinical studies of arrhythmias.

Additionally, because our simulator is based on the ionic channel model, it is easy to incorporate changes in ionic channel properties e.g., in long QT syndrome or during myocardial infarction. Because phenomena such as early afterdepolarization can only be reproduced with a channel-based simulator, our simulator is advantageous in that it is possible to study the contribution of such phenomena on arrythmogenecity.

V. Conclusion

To integrate a large number of data on cardiac electrical properties, we developed a large-scale, three-dimensional simulator of cardiac electrical activity, based on human ventricular geometry and experimentally derived ionic channel models. This simulator has advantages over previous ones in that ventricular fibrillation can be induced with clinical programmed extrastimulation, that fibrillation can be induced more easily by extrastimulation at right ventricular outflow tract as occurs clinically, and that it is possible to examine the contribution of early afterdepolarization to arrhythmogenecity in patients with e.g., long QT syndrome. These advantages indicate that our simulator is useful in supporting a wide range of clinical studies of arrhythmias.

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